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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Regarding: Draft Guidance for industry on "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" [Docket No. 2005D-0112]

Dear Sir or Madam:

With more than 23,000 members worldwide, the American Society of Clinical Oncology (ASCO) is the leading medical society for physicians involved in cancer treatment and research. ASCO members are involved in cancer clinical trials supported by both federal funding sources and the pharmaceutical industry and thus have a strong interest in the subject of this draft Guidance.

ASCO commends the Food and Drug Administration (FDA) staff for producing a very comprehensive and clear document detailing the considerations that should guide sponsors as they design and conduct clinical trials for evaluation of cancer drugs and biologics. In general, the draft Guidance accurately describes the various potential endpoints and the risks and benefits of each in demonstrating clinical benefit that might support product approval.

Notwithstanding the generally high quality of the draft Guidance, ASCO believes there are a few areas that require additional clarification or development. The issues calling for further development are the following:

Patient Reported Outcomes

On pages 12-13, the draft Guidance discusses the challenges posed by endpoints seeking to measure quality of life or general symptom assessment. We understand that this topic has been much debated within FDA and the wider cancer community. Though specific physical signs of symptom management are accepted quality of life measures, to date FDA has not accepted as an appropriate endpoint "broader measures of health-related quality of life" (HRQL). ASCO, however, is not convinced that there are no acceptable patient-reported HRQL measures. One example of a fairly widely accepted HRQL measure is the Functional Assessment of Cancer Therapy-General (FACT-G) scale, and we would encourage FDA to consider FACT-G as well as any other appropriate HRQL measures in its efforts to identify appropriate patient-reported endpoints. ASCO looks forward to review and comment on the draft Guidance referenced on page 12, note 10, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, which FDA reports will be available this summer.

Even if FDA were not yet prepared to make patient reported outcomes the basis for marketing approval, such measures might nevertheless serve an important physician- and patient-information function if they were permitted to be included somewhere in the

product labeling. ASCO urges FDA to consider whether HRQL data might support inclusion in the labeling of supplemental information on quality of life outcomes. Physicians and patients alike have an enhanced interest in quality of life issues for cancer survivors, and there seems little doubt that more information about the full range of symptoms and outcomes confronting survivors would be useful in determining the course of therapy, particularly in the provision of palliative care. ASCO therefore suggests that FDA should not only permit but encourage inclusion of reliable data about patient reported outcomes in the labeling of cancer drugs even if such data might not currently be of the quality or quantity to support initial approval of those drugs.

Placebo Controls

The draft Guidance briefly discusses the circumstances in which placebo controls might be appropriate in cancer clinical trials. In the abstract, placebo controls can be justified when there is no standard therapy for the particular cancer under review. However, there is substantial resistance, especially among cancer patients but also among their health care providers, to the use of a "no-treatment" control, even in the early stage or refractory settings referenced in the draft Guidance. In light of the negative reaction of both patients and physicians to placebo controls for clinical trial participants with cancer, every effort should be made to accommodate the desire for active treatment among all enrolled in cancer clinical trials through the use of aggressive "cross-over" opportunities and perhaps other creative trial designs.

The issue may be of particular concern in connection with drug development programs where accelerated approval is an option, based on response rates or other "surrogate" endpoints. Accelerated approvals are required by law to be confirmed by clinical trials demonstrating a clear clinical benefit, such as survival. ASCO commends FDA for its efforts to compel sponsors to take seriously the requirement of confirmatory trials, which in a setting of unmet need may involve a placebo control (in the form of "best supportive care").
However, when response rates or other surrogate endpoints have been established sufficiently to suggest an accelerated approval, the continued use of a placebo control may be difficult to defend, and patients with no other treatment option should be given access to the investigational agent at the point where accelerated approval seems likely. Thus, even if placebo controls may be necessary in some settings, sponsors and regulators should be alert to opportunities for "cross-over" to active treatment once the placebo controls have served their purpose. We understand that this advice may be consistent with current practice, but it would be useful to physicians and patients alike if the policy were articulated in more detail.

This situation also suggests the role of more concrete FDA guidance to sponsors about procedures for establishing so-called "expanded access" programs to enable those who are ineligible to participate in clinical trials of a new agent that might address their otherwise unmet treatment need. Such programs should be carefully designed to ensure that they do not interfere with the recruitment to clinical trials, nor should they represent an opening for the sponsor to engage in pre-approval promotion by widespread distribution of an as-yet unproven therapy. More specific direction from FDA in connection with expanded access programs would be a service to sponsors, as well as to physicians and patients.

Site-specific Guidances

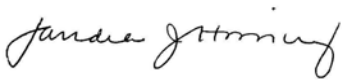
ASCO looks forward to continued collaboration with FDA in the development of site-specific endpoint in the future. One area that may be particularly important for such guidance is hematological cancers, given the intense amount of drug development activity concentrated in those diseases. With all such endpoint considerations, ASCO urges careful consideration of the role that might be played by pharmacogenomics

and other biomarkers. In that connection, ASCO appreciates the recently finalized Guidance on "Pharmacogenomic Data Submissions" and suggest that biomarkers represent another subject that could be developed through a separate Guidance. While we are well aware that use of biomarkers as a surrogate for clinical benefit does not yet have an established scientific basis in any disease, ASCO anticipates that future drug development could be made much more efficient and cost-effective through identification and reliance on valid biomarkers as endpoints in cancer clinical trials.

Conclusion

ASCO is very appreciative of the effort the FDA staff has invested in the recent series of draft Guidances and other information for physicians and patients, as well as for sponsors. These documents serve not only to inform the interested public, but also to initiate dialogue on important topics in drug development and regulation. ASCO welcomes the opportunity to participate in the agency's policy development through the comment process, and applauds the current leadership in the Office of Oncology Drug Products for facilitating this exchange of views.

Sincerely,



Sandra J. Horning, MD
President